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ЕЖЕМЕСЯЧНЫЙ НАУЧНЫЙ ЖУРНАЛ

Медицинские новости Грузии

საქართველოს სამედიცინო სიახლენი

GEORGIAN MEDICAL NEWS

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GMN: Georgian Medical News is peer-reviewed, published monthly journal committed to promoting the science and art of medicine and the betterment of public health, published by the GMN Editorial Board since 1994. GMN carries original scientific articles on medicine, biology and pharmacy, which are of experimental, theoretical and practical character; publishes original research, reviews, commentaries, editorials, essays, medical news, and correspondence in English and Russian.

GMN is indexed in MEDLINE, SCOPUS, PubMed and VINITI Russian Academy of Sciences. The full text content is available through EBSCO databases.

GMN: Медицинские новости Грузии - ежемесячный рецензируемый научный журнал, издаётся Редакционной коллегией с 1994 года на русском и английском языках в целях поддержки медицинской науки и улучшения здравоохранения. В журнале публикуются оригинальные научные статьи в области медицины, биологии и фармации, статьи обзорного характера, научные сообщения, новости медицины и здравоохранения. Журнал индексируется в MEDLINE, отражён в базе данных SCOPUS, PubMed и ВИНИТИ РАН. Полнотекстовые статьи журнала доступны через БД EBSCO.

GMN: Georgian Medical News – საქართველოს სამედიცინო სიახლენი – არის ყოველთვიური სამეცნიერო სამედიცინო რეცენზირებადი ჟურნალი, გამოიცემა 1994 წლიდან, წარმოადგენს სარედაქციო კოლეგიისა და აშშ-ის მეცნიერების, განათლების, ინდუსტრიის, ხელოვნებისა და ბუნებისმეტყველების საერთაშორისო აკადემიის ერთობლივ გამოცემას. GMN-ში რუსულ და ინგლისურ ენებზე ქვეყნდება ექსპერიმენტული, თეორიული და პრაქტიკული ხასიათის ორიგინალური სამეცნიერო სტატიები მედიცინის, ბიოლოგიისა და ფარმაციის სფეროში, მიმოხილვითი ხასიათის სტატიები.

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WEBSITE

www.geomednews.com

К СВЕДЕНИЮ АВТОРОВ!

При направлении статьи в редакцию необходимо соблюдать следующие правила:

1. Статья должна быть представлена в двух экземплярах, на русском или английском языках, напечатанная через **полтора интервала на одной стороне стандартного листа с шириной левого поля в три сантиметра**. Используемый компьютерный шрифт для текста на русском и английском языках - **Times New Roman** (**Кириллица**), для текста на грузинском языке следует использовать **AcadNusx.** Размер шрифта - **12**. К рукописи, напечатанной на компьютере, должен быть приложен CD со статьей.

2. Размер статьи должен быть не менее десяти и не более двадцати страниц машинописи, включая указатель литературы и резюме на английском, русском и грузинском языках.

3. В статье должны быть освещены актуальность данного материала, методы и результаты исследования и их обсуждение.

При представлении в печать научных экспериментальных работ авторы должны указывать вид и количество экспериментальных животных, применявшиеся методы обезболивания и усыпления (в ходе острых опытов).

4. К статье должны быть приложены краткое (на полстраницы) резюме на английском, русском и грузинском языках (включающее следующие разделы: цель исследования, материал и методы, результаты и заключение) и список ключевых слов (key words).

5. Таблицы необходимо представлять в печатной форме. Фотокопии не принимаются. **Все цифровые, итоговые и процентные данные в таблицах должны соответствовать таковым в тексте статьи**. Таблицы и графики должны быть озаглавлены.

6. Фотографии должны быть контрастными, фотокопии с рентгенограмм - в позитивном изображении. Рисунки, чертежи и диаграммы следует озаглавить, пронумеровать и вставить в соответствующее место текста **в tiff формате**.

В подписях к микрофотографиям следует указывать степень увеличения через окуляр или объектив и метод окраски или импрегнации срезов.

7. Фамилии отечественных авторов приводятся в оригинальной транскрипции.

8. При оформлении и направлении статей в журнал МНГ просим авторов соблюдать правила, изложенные в «Единых требованиях к рукописям, представляемым в биомедицинские журналы», принятых Международным комитетом редакторов медицинских журналов - http://www.spinesurgery.ru/files/publish.pdf и http://www.nlm.nih.gov/bsd/uniform_requirements.html
В конце каждой оригинальной статьи приводится библиографический список. В список литературы включаются все материалы, на которые имеются ссылки в тексте. Список составляется в алфавитном порядке и нумеруется. Литературный источник приводится на языке оригинала. В списке литературы сначала приводятся работы, написанные знаками грузинского алфавита, затем кириллицей и латиницей. Ссылки на цитируемые работы в тексте статьи даются в квадратных скобках в виде номера, соответствующего номеру данной работы в списке литературы. Большинство цитированных источников должны быть за последние 5-7 лет.

9. Для получения права на публикацию статья должна иметь от руководителя работы или учреждения визу и сопроводительное отношение, написанные или напечатанные на бланке и заверенные подписью и печатью.

10. В конце статьи должны быть подписи всех авторов, полностью приведены их фамилии, имена и отчества, указаны служебный и домашний номера телефонов и адреса или иные координаты. Количество авторов (соавторов) не должно превышать пяти человек.

11. Редакция оставляет за собой право сокращать и исправлять статьи. Корректура авторам не высылается, вся работа и сверка проводится по авторскому оригиналу.

12. Недопустимо направление в редакцию работ, представленных к печати в иных издательствах или опубликованных в других изданиях.

При нарушении указанных правил статьи не рассматриваются.

REQUIREMENTS

Please note, materials submitted to the Editorial Office Staff are supposed to meet the following requirements:

1. Articles must be provided with a double copy, in English or Russian languages and typed or compu-ter-printed on a single side of standard typing paper, with the left margin of **3** centimeters width, and **1.5** spacing between the lines, typeface - **Times New Roman** (**Cyrillic**), print size - **12** (referring to Georgian and Russian materials). With computer-printed texts please enclose a CD carrying the same file titled with Latin symbols.

2. Size of the article, including index and resume in English, Russian and Georgian languages must be at least 10 pages and not exceed the limit of 20 pages of typed or computer-printed text.

3. Submitted material must include a coverage of a topical subject, research methods, results, and review.

Authors of the scientific-research works must indicate the number of experimental biological species drawn in, list the employed methods of anesthetization and soporific means used during acute tests.

4. Articles must have a short (half page) abstract in English, Russian and Georgian (including the following sections: aim of study, material and methods, results and conclusions) and a list of key words.

5. Tables must be presented in an original typed or computer-printed form, instead of a photocopied version. **Numbers, totals, percentile data on the tables must coincide with those in the texts of the articles.** Tables and graphs must be headed.

6. Photographs are required to be contrasted and must be submitted with doubles. Please number each photograph with a pencil on its back, indicate author's name, title of the article (short version), and mark out its top and bottom parts. Drawings must be accurate, drafts and diagrams drawn in Indian ink (or black ink). Photocopies of the X-ray photographs must be presented in a positive image in **tiff format**.

Accurately numbered subtitles for each illustration must be listed on a separate sheet of paper. In the subtitles for the microphotographs please indicate the ocular and objective lens magnification power, method of coloring or impregnation of the microscopic sections (preparations).

7. Please indicate last names, first and middle initials of the native authors, present names and initials of the foreign authors in the transcription of the original language, enclose in parenthesis corresponding number under which the author is listed in the reference materials.

8. Please follow guidance offered to authors by The International Committee of Medical Journal Editors guidance in its Uniform Requirements for Manuscripts Submitted to Biomedical Journals publication available online at: http://www.nlm.nih.gov/bsd/uniform_requirements.html
http://www.icmje.org/urm_full.pdf
In GMN style for each work cited in the text, a bibliographic reference is given, and this is located at the end of the article under the title "References". All references cited in the text must be listed. The list of references should be arranged alphabetically and then numbered. References are numbered in the text [numbers in square brackets] and in the reference list and numbers are repeated throughout the text as needed. The bibliographic description is given in the language of publication (citations in Georgian script are followed by Cyrillic and Latin).

9. To obtain the rights of publication articles must be accompanied by a visa from the project instructor or the establishment, where the work has been performed, and a reference letter, both written or typed on a special signed form, certified by a stamp or a seal.

10. Articles must be signed by all of the authors at the end, and they must be provided with a list of full names, office and home phone numbers and addresses or other non-office locations where the authors could be reached. The number of the authors (co-authors) must not exceed the limit of 5 people.

11. Editorial Staff reserves the rights to cut down in size and correct the articles. Proof-sheets are not sent out to the authors. The entire editorial and collation work is performed according to the author's original text.

12. Sending in the works that have already been assigned to the press by other Editorial Staffs or have been printed by other publishers is not permissible.

Articles that Fail to Meet the Aforementioned Requirements are not Assigned to be Reviewed.

ავტორთა საყურადღებოდ!

რედაქციაში სტატიის წარმოდგენისას საჭიროა დავიცვათ შემდეგი წესები:

1. სტატია უნდა წარმოადგინოთ 2 ცალად, რუსულ ან ინგლისურ ენებზე,დაბეჭდილი სტანდარტული ფურცლის 1 გვერდზე, 3 სმ სიგანის მარცხენა ველისა და სტრიქონებს შორის 1,5 ინტერვალის დაცვით. გამოყენებული კომპიუტერული შრიფტი რუსულ და ინგლისურენოვან ტექსტებში - **Times New Roman (Кириллица)**, ხოლო ქართულენოვან ტექსტში საჭიროა გამოვიყენოთ **AcadNusx.** შრიფტის ზომა – 12. სტატიას თან უნდა ახლდეს CD სტატიით.

2. სტატიის მოცულობა არ უნდა შეადგენდეს 10 გვერდზე ნაკლებს და 20 გვერდზე მეტს ლიტერატურის სიის და რეზიუმეების (ინგლისურ, რუსულ და ქართულ ენებზე) ჩათვლით.

3. სტატიაში საჭიროა გაშუქდეს: საკითხის აქტუალობა; კვლევის მიზანი; საკვლევი მასალა და გამოყენებული მეთოდები; მიღებული შედეგები და მათი განსჯა. ექსპერიმენტული ხასიათის სტატიების წარმოდგენისას ავტორებმა უნდა მიუთითონ საექსპერიმენტო ცხოველების სახეობა და რაოდენობა; გაუტკივარებისა და დაძინების მეთოდები (მწვავე ცდების პირობებში).

4. სტატიას თან უნდა ახლდეს რეზიუმე ინგლისურ, რუსულ და ქართულ ენებზე არანაკლებ ნახევარი გვერდის მოცულობისა (სათაურის, ავტორების, დაწესებულების მითითებით და უნდა შეიცავდეს შემდეგ განყოფილებებს: მიზანი, მასალა და მეთოდები, შედეგები და დასკვნები; ტექსტუალური ნაწილი არ უნდა იყოს 15 სტრიქონზე ნაკლები) და საკვანძო სიტყვების ჩამონათვალი (key words).

5. ცხრილები საჭიროა წარმოადგინოთ ნაბეჭდი სახით. ყველა ციფრული, შემაჯამებელი და პროცენტული მონაცემები უნდა შეესაბამებოდეს ტექსტში მოყვანილს.

6. ფოტოსურათები უნდა იყოს კონტრასტული; სურათები, ნახაზები, დიაგრამები - დასათაურებული, დანომრილი და სათანადო ადგილას ჩასმული. რენტგენოგრამების ფოტოასლები წარმოადგინეთ პოზიტიური გამოსახულებით **tiff** ფორმატში. მიკროფოტოსურათების წარწერებში საჭიროა მიუთითოთ ოკულარის ან ობიექტივის საშუალებით გადიდების ხარისხი, ანათალების შეღებვის ან იმპრეგნაციის მეთოდი და აღნიშნოთ სურათის ზედა და ქვედა ნაწილები.

7. სამამულო ავტორების გვარები სტატიაში აღინიშნება ინიციალების თანდართვით, უცხოურისა – უცხოური ტრანსკრიპციით.

8. სტატიას თან უნდა ახლდეს ავტორის მიერ გამოყენებული სამამულო და უცხოური შრომების ბიბლიოგრაფიული სია (ბოლო 5-8 წლის სიღრმით). ანბანური წყობით წარმოდგენილ ბიბლიოგრაფიულ სიაში მიუთითეთ ჯერ სამამულო, შემდეგ უცხოელი ავტორები (გვარი, ინიციალები, სტატიის სათაური, ჟურნალის დასახელება, გამოცემის ადგილი, წელი, ჟურნალის №, პირველი და ბოლო გვერდები). მონოგრაფიის შემთხვევაში მიუთითეთ გამოცემის წელი, ადგილი და გვერდების საერთო რაოდენობა. ტექსტში კვადრატულ ფჩხილებში უნდა მიუთითოთ ავტორის შესაბამისი N ლიტერატურის სიის მიხედვით. მიზანშეწონილია, რომ ციტირებული წყაროების უმეტესი ნაწილი იყოს 5-6 წლის სიღრმის.

9. სტატიას თან უნდა ახლდეს: ა) დაწესებულების ან სამეცნიერო ხელმძღვანელის წარდგინება, დამოწმებული ხელმოწერითა და ბეჭდით; ბ) დარგის სპეციალისტის დამოწმებული რეცენზია, რომელშიც მითითებული იქნება საკითხის აქტუალობა, მასალის საკმაობა, მეთოდის სანდოობა, შედეგების სამეცნიერო-პრაქტიკული მნიშვნელობა.

10. სტატიის ბოლოს საჭიროა ყველა ავტორის ხელმოწერა, რომელთა რაოდენობა არ უნდა აღემატებოდეს 5-ს.

11. რედაქცია იტოვებს უფლებას შეასწოროს სტატია. ტექსტზე მუშაობა და შეჯერება ხდება საავტორო ორიგინალის მიხედვით.

12. დაუშვებელია რედაქციაში ისეთი სტატიის წარდგენა, რომელიც დასაბეჭდად წარდგენილი იყო სხვა რედაქციაში ან გამოქვეყნებული იყო სხვა გამოცემებში.

აღნიშნული წესების დარღვევის შემთხვევაში სტატიები არ განიხილება.

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CORRELATIVE ASSOCIATION OF OXYGENATION AND SEPSIS PANELS WITH THE USE OF ACE2 INHIBITORS AND WITHOUT IT IN THE CONDITIONS OF SEPTIC SHOCK IN COVID-19-INFECTED AND NON-INFECTED PATIENTS (COHORT STUDY)

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Abstract.

Introduction: Sepsis-associated hyperlactatemia (SAHL), Lactic acidosis, is a common problem in critically ill patients. The prevalence of Lactic acidosis is estimated to be approximately 1% of all hospitalized nonsurgical patients. The purpose of our study was to reveal possible associations between the level of Lactate with sepsis biomarkers: PCT, IL 6, and PO2 in the presence of ACE 2 inhibitors in Covid-19 infected and non-infected patients with Septic Shock.

Methods: We conducted a cohort study, comparing outcomes of 212 critically ill patients with Septic shock, who were treated in the intensive care unit of First University Clinic of Tbilisi State Medical University during the 2020-2021 years.

Inclusion criteria for the study were: Age>40ys; COVID-19 and other respiratory diseases associated with Septic shock, with respiration dysfunctions with prior exposure to ACE2 inhibitors o no history of treatment with the ACE2 inhibitors.

Patients enrolled in the study were individuals who were diagnosed with COVID–19 infection and septic shock, and who were undergoing treatment with ACE2 inhibitors/not taking ACE2 inhibitors; patients with septic shock who were not infected with COVID-19, and who were undergoing treatment with ACE2 inhibitors/not taking ACE2 inhibitors. According to lactate level, the studied patients were divided into subgroups: lactate <3 mMol/l, and lactate > 3mmol/l.

In patients with septic shock who were not infected with COVID-19 the main Causative microorganisms were gram-negative bacteria.

In patients' blood the Interleukin-6 (IL-6), lactate, procalcitonin (PCT), pO2, and pulmonary pressure were investigated.

Results: Results of the study show that the rise in lactate levels in COVID-19-infected and non-infected patients was accompanied by an increase in PCT content and a decrease in pO2 level in blood. Therefore, serum lactate levels can be used as a prognostic marker of the severity of septic shock in COVID-19-infected and noninfected patients. In COVID-19-infected patients together with the increased lactate level, increases the level of IL-6, which indicates the important link between the quality of immunological disorders, inflammation, and COVID-19 infection in patients with ARDS and sepsis. These alterations were not prevented by the prior use of the ACE2 inhibitors.

Conclusion: In COVID-19-infected and noninfected patients who didn't use ACE2 inhibitors, high lactate levels were accompanied by decreased pulmonary pressure which was normalized in patients who prior used ACE2 inhibitors.

Key words. ACE2 inhibitors, lactate, septic shock, Covid-19.

Introduction.

Sepsis-associated hyperlactatemia (SAHL), Lactic acidosis, is a common problem in critically ill patients. The prevalence of Lactic acidosis is approximately 1% of all hospitalized nonsurgical patients. Since it is associated with a high mortality rate, critical care physicians need to be adept at diagnosing and treating this grave clinical condition [1-3].

In sepsis, there may be observed an increased production of lactate even in the absence of hypoxia. Hyperlactatemia may be caused both by oxygen debt at inadequate tissue perfusion and may be promoted by endotoxin-induced inhibition of pyruvate dehydrogenase activity or by damaged oxidative phosphorylation, increased anaerobic glycolysis, leading to pyruvate and lactate accumulation in the cell, with consequent leakage of excess lactate into the circulation, causing an increase in blood lactate level [4,5].

COVID-19 is a localized "respiratory infection" and a "multisystem disease" caused by diffuse systemic processes involving complex interactions of immunological, inflammatory, and coagulation cascades. The SARS-CoV-2 itself can cause sepsis regardless of the presence of secondary bacterial or fungal infections [6] through various mechanisms, including immune dysregulation, and respiratory dysfunction, which in the conditions of circulatory dysfunction and disorders of microcirculation, leading to hypoxia, hypoxemia, metabolic acidosis, and the multiorgan failure observed in COVID-19 [6,7].

Pulmonary arterial hypertension, defined as a mean pulmonary artery pressure exceeding 20 mmHg, is usually observed in human sepsis, even before the development of acute respiratory distress syndrome (ARDS). Pulmonary arterial hypertension during sepsis and ARDS was associated with obstruction of the pulmonary microcirculation with microthrombi composed of platelets and leukocytes, and also with active pulmonary vasoconstriction induced by the autonomous nervous system, hypoxia or vasoactive humoral factors ("mediators") [8,9]. Elevated pulmonary vascular pressure, due to pulmonary vasoconstriction and vascular remodeling, opposes blood flow through the lungs thus limiting the ability of the right ventricle (RV) to increase cardiac output (CO) and maintain adequate oxygen delivery to tissue. Although the exact cause of pulmonary arterial hypertension in sepsis is unknown, it is associated with high mortality [8-10].

The renin-angiotensin system (RAS) is a complex endocrine system with a multi-dimensional enzymatic cascade to keep arterial blood pressure constant, which in turn helps maintain tissue perfusion and extracellular volume [4,11,12]. Although

RAS activation is a physiological reaction counteracting septic shock, excessive activation may further aggravate pro-inflammatory responses and vascular dysfunction, resulting in worse clinical outcomes. In particular, a high degree of RAS activation was associated with microvascular dysfunction and organ failure in patients with sepsis [12,13]. Conversely, the inactivation of RAS showed protective effects on acute pulmonary or renal injury and decreased endotoxin-induced oxidative stress and endothelial dysfunction [10,14,15]. In animal models, the inhibition of angiotensin II improved mortality due to sepsis [16]. Accordingly, chronic suppression of RAS before an event of sepsis may be beneficial for clinical outcomes. One human observational study reported that the 30-day mortality rate due to sepsis was reduced in elderly male patients who ever received Angiotensin II receptor blockers (ARBs) [13,17]. However, there is a lack of evidence evaluating the relationship between RAS suppression before an event of sepsis, and clinical prognoses. There have been several studies to evaluate whether ACE inhibitors or ARBs can be beneficial in sepsis [13,18,19].

For diagnosis of sepsis, several potential blood biomarkers are considered for sepsis diagnosis, among which, interleukin 6 (IL-6), Procalcitonin (PCT), and C-reactive protein (CRP) are most widely used in clinical routine [18,20]. Normally, PCT is produced by C-cells in the thyroid gland. In the case of systemic bacterial infection, PCT is also produced in many non-thyroidal cells, and the levels of PCT dramatically increase within a few hours [21]. In patients with sepsis, IL-6 values were also found elevated persistently [20].

The aim of our study was to identify possible diagnostic markers of the severity condition of the patients with ARDS and septic shock. For this purpose, we investigated the possible dependence between the level of Lactate and sepsis biomarkers (PCT, IL-6, and pO2) (in the presence and without ACE2 inhibitors) in COVID-19-infected and non-infected patients.

Materials and Methods.

We conducted a cohort study of 212 critically ill patients with Septic shock (134 men (63.3%) and 78 women (36.7%), with a mean age between 40-70 years were evaluated), who were treated in the intensive care unit of First University Clinic of Tbilisi State Medical University during 2020-2021 years.

Inclusion criteria for the study were: Age>40ys; COVID-19 and/or other respiratory diseases associated with Septic shock, with respiration dysfunctions with prior exposure to ACE2 inhibitors or no history of treatment with the ACE2 inhibitors.

Exclusion criteria: Age< 40 years; absence of respiratory dysfunction.

Patients enrolled in the study were divided into 4 target groups: Group I comprised individuals who were diagnosed with COVID–19 infection and septic shock and were undergoing treatment with ACE2 inhibitors. Group 2 patients were those who were diagnosed with COVID-19 infection and septic shock and were not taking ACE 2 inhibitors. Group 3 included patients with septic shock who were not infected with COVID-19 and were undergoing treatment with ACE2 inhibitors. Group 4 comprised patients diagnosed with septic shock who were not infected with COVID-19 and were not taking ACE 2 inhibitors. According to lactate level, the studied patients were divided into subgroups: Groups 1a, 2a, 3a, 4a - whose lactate was <3mmol/l, and 1b, 2b, 3, 4b - whose lactate was> 3mmol/l.

In patients with septic shock who were not infected with COVID-19 (Groups 3, 4) the main causative microorganisms were gram-negative bacteria.

Laboratory tests.

In the patients' blood, we evaluated changes in variables such as Interleukin-6 (IL-6; Norm - < 17.4Pg/ml), lactate (Norm - 1.5-2.2mmol/l), and PCT (Norm - < 0.05 ng/ml). The level of IL-6 concentration in the blood by the electro-chemiluminescence (ECL) method on the Cobas e-411 (Roche) device with Elecsys IL-6 reagent; PCT was measured by immunofluorescence method using a Fin care III Plus device. Lactate was measured by spectro-photocolorometric method, on the biochemical analyzer Cobas C 111. pO2 by radiometric cartridge method with t ABL 90 FLEX (RADIOMETER) device. The pulmonary arterial pressure was measured by GE Vivid s5 Ultrasound Machine (Norm 21 ± 4 mm Hg).

Statistical Methods.

For comparative analysis of the data, we used Factorial Analysis of Variance (We used the Software Program SPSS-12 for Windows to process the data and visualize the results). Statistically significant differences between parameters were assumed; p<0,005 was considered statistically reliable.

Results.

According to the results of our study in COVID-19-infected and non-infected patients who didn't use ACE2 inhibitors difference in lactate level was not detected, though in COVID-19 non-infected patients who used ACE2 inhibitors the level of lactate increased up to 7mmol/l (The normal range is 0.5-2.2mmol/l) (Figure 1).

In COVID-19-infected and non-infected patients, who used ACE2 inhibitors the level of PCT was the lactate level dependent - if the lactate level was high, the PCT level was also

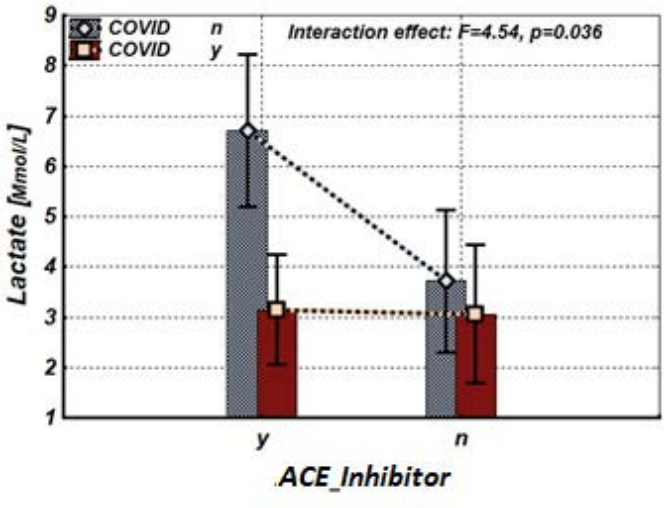

Figure 1. *The impact of ACE2 inhibitors on the lactate level in COVID-19 infected and non-infected patients. (The mean value, Standard deviation, and Confidence interval of 95 %).*

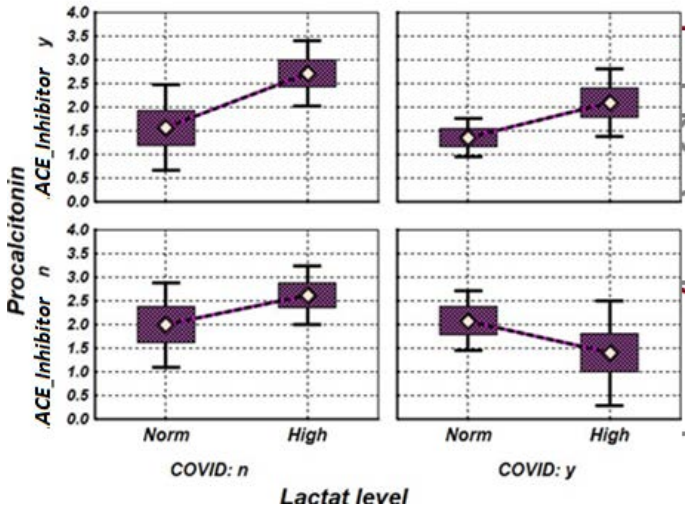

Figure 2. *Dependence of PCT on lactate level in COVID-19 positive and negative patients, with or without prior use of ACE2 inhibitors. (The mean value, Standard deviation, and Confidence interval of 95 %).*

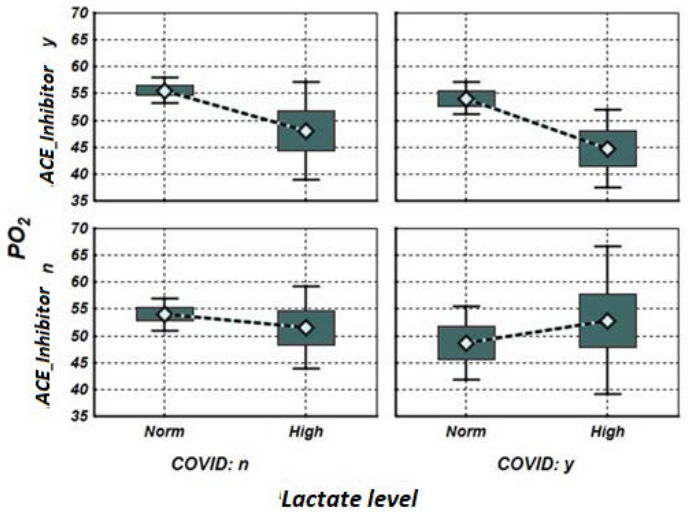

Figure 3. *Dependence of pO_2 on the lactate level in COVID-19 positive and negative patients, with or without prior use of ACE2 inhibitors. (The mean value, Standard deviation, and Confidence interval of 95 %).*

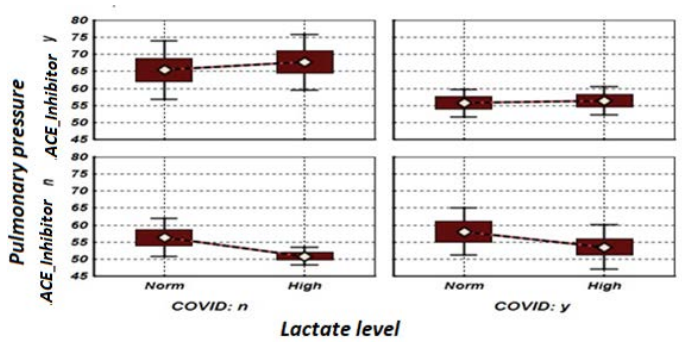

Figure 4. *Dependence of Pulmonary pressure on the lactate level in COVID-19 positive and negative patients, with or without prior use of ACE2 inhibitors. (The mean value, Standard deviation, and Confidence interval of 95 %).*

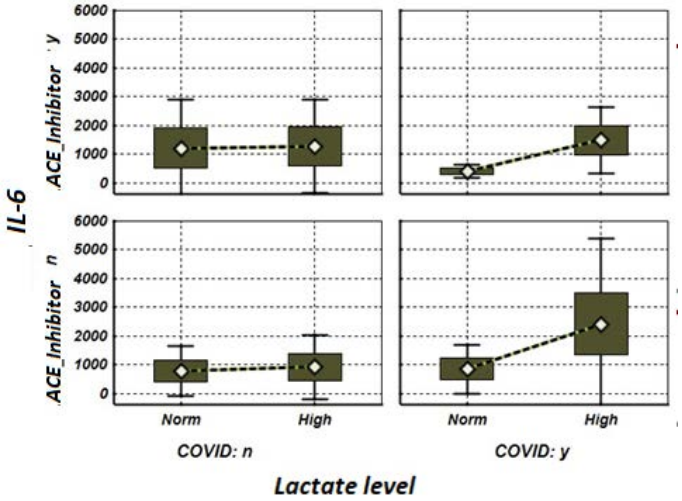

Figure 5. *Dependence of IL-6 on the lactate level in COVID-19 positive and negative patients, with or without prior use of ACE 2 inhibitors. (The mean value, Standard deviation, and Confidence interval of 95 %).*

Table 1. *Groups of studied patients.*

		Lactate level	ACE2 inhibitor
Group 1 COVID-19-infected patients	Group 1a	<3mmol/l	+
	Group 1b	>3mmol/l	+
Group 2 COVID-19-infected patients	Group 2a	<3mmol/l	-
	Group 2b	>3mmol/l	-
Group 3 COVID-19-noninfected patients	Group 3a	<3mmol/l	+
	Group 3b	>3mmol/l	+
Group 4 COVID-19-noninfected patients	Group 4a	<3mmol/l	_
	Group 4b	>3mmol/l	_

high. Without the use of ACE2 inhibitors, there was no relation between the lactate level and PCT (Figure 2).

In COVID-19-infected and non-infected patients, who used ACE2 inhibitors, pO2 was dependent on the level of lactate - if the lactate level was high, the pO2 level was low. Without the prior use of ACE2 inhibitors, there was no relation between pO2 and lactate level (Figure 3).

As it seems from the study results, in all investigated patients pulmonary hypertension (>20 mmHg) was detected. In patients who didn't use priorly ACE2 inhibitors, the level of pulmonary pressure was lactate level dependent – if the lactate level was high, the pulmonary pressure decreased significantly, especially in COVID-19-negative patients. In the case of the use of an ACE2 inhibitor, there was no relation between pulmonary pressure and lactate level (Figure 4).

In COVID-19-infected patients, the level of IL-6 was Lactate level dependent – IL-6 content increased with the increase of the lactate level, especially, in the case of the prior use of the ACE2 inhibitors. In COVID-19-non-infected patients, the level of IL-6 did not change despite the changes in lactate level (Figure 5).

Discussion.

Serum lactate levels usually are used as a surrogate marker of tissue hypoxia in critically ill patients, also reflect the

progression of septic shock and, therefore, may be used as a noninvasive prognostic marker or guide to resuscitation. Some studies demonstrated hyperlactatemia in patients with ARDS that were proportional to the severity of the lung injury, several studies indicate that there is no significant relation between lactate levels and the severity of lung disease [12,22].

We investigated the lactate level in the patient's blood with ARDS and sepsis (COVID-19-infected and non-infected). According to the results of the presented study, alterations of the lactate level in COVID-19-infected and non-infected patients with ARDS and sepsis were dependent on the previous history of use of ACE2 inhibitors: in patients, who didn't priory use ACE2 inhibitors difference in lactate level between COVID-19-infected and non-infected patients was not detected; in patients who used ACE2 inhibitors the level of lactate in COVID-19 non-infected patients was importantly higher than in COVID-19-infected patients.

In sepsis, increased production of lactate may be caused both by oxygen debt at inadequate tissue perfusion and endotoxin-induced inhibition of pyruvate dehydrogenase activity or by damaged oxidative phosphorylation, and increased anaerobic glycolysis; disorders in mitochondrial respiration, activation of anaerobic glycolysis in the tissue cells, and accumulation of lactate in the blood may be induced by Ang II, initiating the inflammatory cascade [2,24,26]. Therefore, the prior use of ACE2 inhibitors can support the decrease of Ang II level and its pro-inflammatory cascade, in particular, disorders in the mitochondrial respiratory chain, in critically ill COVID-19-infected and non-infected patients with septic shock [19,27,28].

It is believed, SARS-COV enters alveolar cells via a membrane-bound angiotensin-converting enzyme 2 (ACE2), which is the binding site for the coronavirus spike protein, promoting its adhesion to the cell surface, followed by internalization of the SARS-COV/ACE2 complex into the cytoplasm which reduces ACE2 expression on the membrane surface [11,23,24], leads to the increase of Ang II level, Ang II-induced ROS formation [24-26], and inclusion of inflammation. These effects are the additional source, promoting disorders in mitochondrial respiration and activation of anaerobic glycolysis in the tissue cells, and accumulation of lactate in the blood. In our previous studies it was shown that in patients infected with COVID-19 with ARDS and sepsis who did not receive ACE2 inhibitors, the initial level of Ang II was higher than in non-infected patients [19,27]. In COVID-19-infected and uninfected patients with ARDS and sepsis, ACE2 inhibitors reduce the levels of Ang II and the severity of inflammation (CRP, IL-6, the activity of leukocytes and blood pro-coagulation system (level of D dimer), and therefore, the ACE2 inhibitors play an important role in the regulation of inflammatory processes in both COVID-19-infected and non-infected patients with septic shock [19,27,28].

According to the results of the presented study, in COVID-19-infected and non-infected patients with ARDS and sepsis who didn't use ACE2 inhibitors difference in lactate level was not detected; in COVID-19 non-infected patients who used ACE2 inhibitors, the level of lactate was importantly higher than in COVID-19-infected patients. According to the literature data, intracellular ANG II plays an important role in the regulation of mammalian cell function and is involved in the pathogenesis of various human diseases. ANG II through nuclear AT1Rs promotes protective mechanisms by stimulating the AT2R signaling cascade, which involves mitochondrial AT2Rs and Mas receptors. The stimulation of nuclear ANG II receptors enhances mitochondrial biogenesis thus protecting the cell against oxidative stress. These studies indicate that iRAS promotes the protection of cells through nuclear AT1R signaling, which, in turn, promotes AT2R-dependent processes in mitochondria [29].

The rice in lactate level in COVID-19-infected and non-infected patients is accompanied by an increase in PCT content and a decrease in pO2 level. In COVID-19-infected patients together with the increased lactate level, the level of IL-6 increases, which indicates the important link between the quality of immunological disorders and inflammation and CPVID-19 infection in patients with ARDS and sepsis. Therefore, lactate level reflects the severity of inflammation in patients with ARDS and septic shock. These alterations cannot be prevented by ACE2 inhibitors.

In COVID-19-infected and noninfected patients who didn't use ACE2 inhibitors, high lactate levels were accompanied by decreased pulmonary pressure which was normalized in patients who prior used ACE2 inhibitors.

Conclusion.

Serum lactate levels can be used as a prognostic marker of the severity of septic shock in COVID-19-infected and noninfected patients. The rice in lactate level in COVID-19-infected and non-infected patients is accompanied by an increase in PCT content and a decrease in pO2 level. In COVID-19-infected patients together with the increased lactate level, the level of IL-6 increases, which indicates the important link between the quality of immunological disorders and inflammation and COVID-19 infection in patients with ARDS and sepsis. These alterations cannot be prevented by ACE2 inhibitors.

In COVID-19-infected and noninfected patients who didn't use ACE2 inhibitors, high lactate levels were accompanied by decreased pulmonary pressure which was normalized in patients who prior used ACE2 inhibitors.

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